



Express Mail No. EM 146 907 103 US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Rein *et al.*

Confirmation No.: 8812

Application No.: 09/980,727

Art Unit: 1618

Filed: July 8, 2002

Examiner: Rogers, James William

For: METHOD FOR PRODUCING A WATER-
INSOLUBLE AMORPHOUS OR PARTIALLY
AMORPHOUS CONTROLLED RELEASE
MATRIX

Attorney Docket No: 11390-009

PRE-APPEAL BRIEF CONFERENCE REQUEST

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicants hereby request review of the Final Rejection mailed October 19, 2009 ("Final Rejection") of the above-captioned application prior to filing an appeal brief for the reasons set forth below. Applicants submit that the Final Rejection fails to establish a *prima facie* rejection for anticipation and obviousness. Submitted herewith is (i) a Notice of Appeal accompanied by the appropriate fee, and (ii) a Petition for an Extension of Time for three (3) months from January 19, 2010 to March 19, 2010 accompanied by the appropriate fee.

The present invention is directed to controlled release matrices, and to methods for producing a such controlled release matrices, wherein the method comprises co-extruding through an extruder a composition comprising a dry mixture of at least one pharmaceutically active agent and at least one starch, wherein the temperature at the orifice of the extruder during the extrusion process is below 100°C under normal pressure, and wherein the co-extruding is under sheer force, temperature and pressure conditions such that the starch in the extruded controlled release matrix is vitrified, and wherein up to 15% by weight water is added to the composition prior to co-extruding.

1. Claims 10, 16-18 and 23-32 are rejected under 35 U.S.C. § 102(b), allegedly, as anticipated by European Patent Application Publication No. 0 580 860 A1 to Nakamichi *et al.* ("Nakamichi"). Applicants respectfully disagree with the Examiner's allegation. As Applicants discussed previously, the solid dispersions of Nakamichi are not controlled released dispersions and are not vitrified, which is each required by the pending claims. With regard to the Examiner's citation to test example 7, Applicants note that the formulation of test example 7 is found in the description of

Example 5 on page 7, lines 49-55 of Nakamichi, which indicates that the compositions tested contained 5% (w/w) triacetin, a plasticizer used to lower the transition temperature of a polymer (see Nakamichi at page 3, lines 33-46). The controlled release matrices of the present invention do not contain a plasticizer, or any other type of compound used to lower the transition temperature of a polymer. Thus, not only do the controlled release matrices of the present claims differ from those of Nakamichi by being vitrified, they differ in that they do not contain a plasticizer to lower the transition temperature of a polymer. In order for a reference to anticipate a claim, each and every element of the claim must be disclosed in that one reference. *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565 (Fed. Cir. 1985). "Anticipation under Section 102 can be found only if a reference shows exactly what is claimed. . ." *Structural Rubber Prod. Co. v. Park Rubber Co.*, 749 F.2d 707 (Fed. Cir. 1984). None of the pending claims is explicitly anticipated by the disclosure of Nakamichi since none of the solid dispersions taught by Nakamichi are vitrified, controlled release dispersions. With regard to the Examiner's comments on the release profiles in the buffers at two different pH values being different from that in the body, Applicants point out the reason why two different pH values are used is because the solid dispersions being tested are enteric coated dispersions. As is understood by those of skill in the art, enteric coated dispersions are meant to protect the active agent from being released in the stomach, *i.e.*, at low pH.

In view of the foregoing, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 102(b) in view of Nakamichi.

2. Claims 10, 16, 17, and 23-32 are rejected under 35 U.S.C. § 102(b), allegedly, as anticipated by International Patent Publication No. WO 92/15285 to Lentz *et al.* ("Lentz"). Applicants respectfully disagree and note that none of the rejected claims, directed to controlled release matrices, is explicitly anticipated by the disclosure of Lentz since Lentz does not disclose such controlled release matrices. Applicants maintain their position that the Examiner is improperly combining one teaching of Lentz with regard to processing starch and combining the processed starch with an active agent and the teaching in Lentz with regard to co-extruding previously processed starch with an active agent. The present claims are limited to compositions produced by co-extrusion which are different from the sole co-extruded composition of Lentz. The Examiner asserts that this example is not meant to be limiting, but Applicants assert that it fully exemplifies the disclosure of Lentz with regard to co-extruding a pharmaceutically active agent with the molecularly dispersed starch (MDS) taught in Lentz. Even though both Lentz and the present invention teach destructure of starch by way of extrusion, the nature of the destructured starch obtained is different since the molecularly dispersed starch of Lentz is soft and rubbery and, thus, above glass transition temperature. In fact, Lentz teaches at page 14, lines 6-25, that it is preferred that the process heats the starch above the glass transition temperature. Moreover, Applicants invite the Examiner's attention to page 12, lines

5-25 of Lentz, which discusses that the formation of molecularly dispersed starch (MDS) requires that the starch being melted above its glass transition temperature. It is this MDS that Lentz co-extrudes.

In contrast, the extruded matrices obtained by the present invention are vitrified, *i.e.*, rigid and, thus, their temperature never exceeded the glass transition temperature and preferably remains below the glass transition temperature, as specified in the claims.

Moreover, Applicants invite the Examiner's attention to Figure 6 of Lentz. Figure 6 shows that when the water content is less than 15.8%, the tablets are no longer controlled release tablets. This is in contrast to the presently pending claims which require that the water content be 15% or less. Thus, Lentz does not disclose controlled release compositions with water content as specified in the claims of the instant application.

In view of the foregoing, Applicants submit that the claimed co-extruded compositions are not anticipated by Lentz, and, therefore, respectfully maintain their request that this Section 102(b) rejection be withdrawn.

3. Claims 1, 5, 6, 10, 16-18, 20-32 are rejected under 35 U.S.C. § 103(a), allegedly, as obvious over European Patent Application Publication No. 0 580 860 A1 to Nakamichi *et al.* ("Nakamichi"). The Examiner alleges that Nakamichi is silent on certain parameters of the extrusion process but that it would have been obvious for one skilled in the art to optimize such parameters to obtain the desired product. Applicants respectfully disagree with the Examiner's allegation. A finding of obviousness requires that "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. §103(a). In *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 U.S.P.Q.2d 1385 (2007), the Supreme Court stated that the following factors set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q.2d 459 (1966) still control an obviousness inquiry: (1) the scope and content of the prior art; (2) the differences between the prior art and the claimed invention; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *KSR*, 127 S.Ct. at 1734, 82 U.S.P.Q.2d at 1388 (quoting *Graham*, 383 U.S. at 17-18, 14 U.S.P.Q. at 467).

In order to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974). Moreover, a recent post-*KSR* Federal Circuit decision explained that a non-rigid "flexible TSM test remains the primary guarantor against a non-statutory hindsight analysis" and assures that the obviousness test proceeds on the basis of evidence that arise before the time of invention as the statute requires. *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, 520 F.3d 1358, 1364-65 (Fed. Cir. 2008) (citing *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007)).

In the instant application, the claims are directed to methods of co-extrusion under specified conditions and to the controlled release matrices that result from the methods of co-extrusion. While

Applicants would not dispute that, in certain instances, the optimization of a parameter would be obvious; however, only in cases where the cited prior art teaches not only which parameter to optimize, but also what is the desired product. Applicants submit that the claimed invention is not obvious in view of Nakamichi since Nakamichi does not provide the skilled artisan with the teaching or suggestion of the product to be obtained or the teaching or suggestion of which extrusion parameters to adjust and how to adjust said parameters to achieve the desired product. In the instant case, Nakamichi does not teach or suggest which of the many parameters should be adjusted, if any, *e.g.*, temperature, pressure, amount of water, *etc.*, to achieve the desired result, and Nakamichi does not teach or suggest that a controlled release matrix or a method of obtaining such a controlled release matrix are the desired product. Applicants submit that it would be undue experimentation to try to achieve the claimed invention based on the teachings of Nakamichi. Nakamichi does not provide the person of skill in the art the required reasonable expectation of success to achieve the co-extrusion methods and controlled release compositions claimed in the present application, thus, Nakamichi does not render the claimed invention obvious.

In view of the foregoing, Applicants respectfully maintain their request that the rejection under Section 103(a) in view of Nakamichi be withdrawn.

4. Claims 1, 5, 6, 10, 16-18, 20-32 are rejected under 35 U.S.C. § 103(a), allegedly, as anticipated by International Patent Publication No. WO 92/15285 to Lentz *et al.* (“Lentz”). Applicants respectfully disagree.

Applicants, in order not to burden the record, hereby incorporate by reference their remarks made previously with regard to the teachings of Lentz, including the Declaration of Dr. Rein, and address the Examiner’s comments made in the current office action.

Applicants note that the Examiner’s use of the specific examples in Figure 10, Applicants point out that the claimed methods specifically recite temperatures below 100°C. Thus, three of the four specific examples in Figure 10 of Lentz, 160°C, 130°C, and 100°C, fall outside the claims, not two as alleged by the Examiner. Further, the sole temperature below 100°C in Figure 10 is 70°C. However, this temperature does not produce a controlled release matrix, but rather a quick release dispersion. Thus, Lentz teaches that extrusion at the sole temperature that falls within the claims produces a quick release dispersion, not a controlled release dispersion. Based on this example, Applicants submit that Lentz also teaches away from the claimed invention. Moreover, Applicants note that starch extruded in the experiment summarized in Figure 10 is MDS starch, which starch is not vitrified, as discussed below.

The Examiner is invited to page 12, lines 5-25 of Lentz, which teaches three different temperature levels for three different levels of destructuralization of starch, and that the third level involving the highest temperatures, where the glass transition temperature is exceeded, results in the production of molecularly dispersed starch (MDS), and which can result in a controlled release

dispersion. As previously discussed, the MDS taught in Lentz is not vitrified, and this passage on page 12 clearly indicates that the MDS of Lentz can not be vitrified since the glass transition temperature has been exceeded in producing the MDS. The pending claims require that the matrix produced by the method be a vitrified controlled release matrix, *i.e.*, glassy. Applicants do not find it reasonable to interpret the disclosure of Lentz to include the teaching or suggestion of a controlled-release product produced by co-extrusion below 100°C. Lentz does not teach or suggest a modification of its disclosed method requiring that the temperature at the orifice of the extruder (as well as all other parts of the extruder) during the extrusion process be below 100°C under normal pressure. Indeed, the only disclosed specific experimental conditions for processing starch are found in Example 1 of Lentz and the molecularly dispersed starch (MDS) produced in Example 1 is used throughout all other experiments, including the co-extrusion experiment in Example 18. Applicants submit that the MDS produced according to Example 1 is, indeed, representative of the MDS used in all other experiments disclosed in Lentz, which MDS is not the same as nor suggestive of the co-extruded compositions of the present invention, since the glass transition of the starch was exceeded in producing the MDS, which means that MDS is not vitrified starch. Applicants maintain the position that it is unreasonable for the Examiner to extrapolate the disclosure of Lentz to suggest the co-extrusion of starch and an active agent at a die temperature of less than 100°C.

In view of the foregoing, Applicants respectfully maintain their request that the rejection under Section 103(a) in view of Lentz be withdrawn.

CONCLUSION

For the reasons above, Applicants respectfully submit that presently pending claims 1, 5, 6, 10, 16-18 and 20-32 meet all requirements for patentability and respectfully request allowance and action for issuance. Applicants request that the Examiner call William J. Thomann at (212) 326-3939 if any questions or issues remain.

Respectfully submitted,

Date: March 18, 2010

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